CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761173Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 113717

MEETING MINUTES

Fresenius Kabi SwissBioSim GmbH
Attention: Navayath Shobana, PhD
US Agent
801 Pennsylvania Ave NW #255
Washington, DC 20004

Dear Dr. Shobana:[1]

Please refer to your investigational new drug application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for MSB11455.

We also refer to the meeting between representatives of your firm and the FDA on October 31, 2019. The purpose of the meeting was to discuss aspects of your proposed BLA submission.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Michael Gwathmey, Regulatory Project Manager at (301) 796-8498.

Sincerely,

{See appended electronic signature page}

Kathy Robie Suh, MD, PhD
Clinical Team Leader
Division of Hematology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure:

- Meeting Minutes

[1] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

MEMORANDUM OF MEETING MINUTES

Meeting Type: Biosimilar
Meeting Category: Biosimilar Biological Product Development (BPD) Type 4

Meeting Date and Time: October 31, 2019, 2:00 PM – 3:00 PM ET
Meeting Location: White Oak Building 22, Conference Room: 1313

Application Number: IND 113717
Product Name: MSB11455

Indication: MSB11455 is being developed for the same indications as approved for US-licensed Neulasta (pegfilgrastim)
Sponsor Name: Fresenius Kabi SwissBioSim GmbH

Meeting Chair: Kathy Robie Suh, MD, PhD
Meeting Recorder: Michael Gwathmey, RN

FDA ATTENDEES

Office of Drug Evaluation I, Division of Hematology Products
Albert Deisseroth, MD, PhD, Supervisory Associate Division Director
Kathy Robie Suh, MD, PhD, Clinical Team Leader
Salah Ayache, MD, Clinical Reviewer
Michael Gwathmey, RN, Regulatory Project Manager

Office of Clinical Pharmacology, Division of Clinical Pharmacology V
Salaheldin Hamed, PhD, Team Leader

Office of Biostatistics, Division of Biometrics V
Jingjing Ye, PhD, Team Leader
Wenjuan Gu, PhD, Statistical Reviewer

Office of Process and Facilities (OPF)/Division of Microbiology Assessment
Patricia Hughes, PhD, Branch Chief
Maxwell Van-Tassell, PhD, Microbiology Reviewer

Office of Biotechnology Products (OBP)
Emanuela Lacana, PhD, Associate Director Biosimilar and Biologics Policy

OBP, Division of Biotechnology Review and Research II
Yan Wang, PhD, Team Leader
Pick-Wei Lau, PhD, Product Quality Reviewer

Office of Therapeutic Biologics and Biosimilars
Stacey Ricci, MEng, ScD, Acting Director Scientific Review Staff
Nina Brahme, PhD, MPH, Reviewer
Tom Herndon, MD, Reviewer

Eastern Research Group, Inc.
Christopher A. Sese

SPONSOR ATTENDEES

Fresenius Kabi SwissBioSim GmbH
Ina Frank, Senior Director, Head of Regulatory Affairs
Emilien Gantelet, Senior Manager, Global Regulatory Affairs
Laura Salazar-Fontana, Director, Global Regulatory Affairs, CMC
Navayath Shobana, Director, Global Regulatory Affairs
Fabien Vaudant, Senior Director, Program Lead
Laurent Chevalet, Senior Director, Analytical & Pharmaceutical Development
Gudrun Bachmann, Director, Head of CMC Leads
Alison Sykes, Director, Physicochemical CMC Development
Louise Ingram, Director, Downstream Process Development
Radmila Kanceva, Senior Director, Head of Clinical Development
Michael Stahl, Bioanalytical Scientist
Dara Corrigan, Vice President, Government Affairs and Policy
Georg Feger, SVP, Head of Research, Development, Manufacturing & Supply
Michael Soldan, Executive Vice President, Biosimilars, Head of Biosimilars

1.0 BACKGROUND

The sponsor requested a BPD Type 4 meeting to seek FDA's input on the development program for MSB11455 (a proposed biosimilar to US-licensed Neulasta) as well as feedback on their proposed BLA submission. The proposed indications of MSB11455 are the same indications as approved for US-licensed Neulasta (pegfilgrastim).

FDA may provide further clarifications of, or refinements and/or changes to these preliminary responses and the advice provided at the meeting based on further information provided by Fresenius Kabi SwissBioSim GmbH and as the Agency's thinking evolves on certain statutory provisions regarding applications submitted under section 351(k) of the Public Health Service Act (PHS Act).

2.0 DISCUSSION

Preamble comment: We note that you have not submitted comprehensive comparative analytical data to allow the Agency to make a preliminary evaluation of analytical similarity between MSB11455 and U.S.- licensed Neulasta. Considering that in earlier

meetings FDA noted some differences between MSB11455 and U.S.-licensed Neulasta, we highly recommend that you request a Type 3 meeting prior to your planned BLA submission to allow an in-depth data review and advice regarding your ongoing MSB11455 development program. Please refer to FDA Guidance for Industry "Formal Meetings Between the FDA and Sponsors or Applicants of BsUFA Products" (June 2018).

Discussion: **Fresenius provided a summary of the preliminary comparative analytical assessment data provided in the previous BPD Type-2 meeting in April 2019. Fresenius also provided a plan for additional data to be included in the BLA submission to support a demonstration that MSB11455 is highly similar to U.S.-Neulasta. Fresenius requested an explanation of the Agency's reasons for recommending a BPD Type-3 meeting. The Agency stated that it was not clear from the information provided in the meeting package, whether the MSB11455 lots used in the preliminary analytical similarity studies were manufactured using processes representative of the commercial process, and whether these lots were analytically comparable. It also appeared that V 2.0 process includes multiple changes that seem significant, and Fresenius had not submitted comparability data. Therefore, the Agency considered that the preliminary analytical similarity data provided in April 2019 may not be comprehensive, and recommended a BPD Type-3 meeting to allow for a comprehensive review of the data generated by Fresenius, and to provide additional feedback on the MSB11455 development program. The Agency clarified that the BPD Type-3 meeting was a recommendation, but is optional and not a requirement prior to submission of the BLA. Fresenius explained that they analyzed quantitative attributes using a quality ranges approach by comparing the min-max of MSB11455 lots to the mean ± 3SD of U.S.-Neulasta lots. The Agency expressed concern about this data analysis approach for the comparative analytical assessment. The Agency reminded Fresenius to provide justifications for their data analysis method.**

Post-Meeting Comment: **We refer you to the draft guidance for industry entitled, "Development of Therapeutic Protein Biosimilars: Comparative Analytical Assessment and Other Quality-Related Considerations," (May 2019) regarding quantitative analyses using the quality range approach.**

Question 1: *The manufacturing processes for G-CSF Intermediate, MSB11455 drug substance (MSB11455- DS) and MSB11455 drug product (MSB11455-DP) have been validated at three different sites:* (b) (4)

An overview of the process validation, and batch analyses for PPQ batches will be included in the BLA.

(b) (4)

(b) (4)

An overview of the process validation of G-CSF Intermediate, MSB11455-DS and MSB11455-DP are provided under section Supportive Data. Process validation of MSB11455-DP is further discussed below focusing on microbial control and shipping validation topics.

a. *Does the Agency agree with the proposed approach to support microbiological control of MSB11455-DP?*

b. *The Company has completed comprehensive simulated shipping studies to demonstrate quality and sterility integrity of the pre-filled syringe drug product in the intended commercial pack during transportation. Does the Agency agree that these studies are sufficient to ensure integrity of MSB11455 DP during transportation?*

FDA Response to Question 1: The Agency has the following comments regarding the proposed microbiological control strategy:

(b) (4)

We do not agree that the presented studies are sufficient to ensure integrity of MSB11455 drug product (DP) during transportation.

1. Regarding your simulated shipping studies, we have the following comments:

i. You did not provide information on how your simulated shipping studies are representative of your real time shipping. The simulated conditions should be fully representative of the type, sequence, duration, and intensity of each stress or combination of stresses expected during real-time shipping conditions. Provide the detailed information to justify that your simulated shipping studies are representative of your real time shipping conditions in your BLA submission.

ii. You provided the shipping simulation study results in Table 29 in the meeting package. From product quality perspective, although the data appear acceptable, it is not clear if the DP samples used in the studies are fully representative of your final commercial DP, and if all stability indicating quality attributes are evaluated. Provide this information in your BLA submission to support your commercial DP stability under the real time shipping conditions.

2. The information and data provided for the shipping container in the simulated shipping studies is insufficient. To qualify your shipping containers, you need to assess whether the commercial shipping containers used are suitable for maintaining the target product temperature when exposed to relative environmental conditions (e.g., different climate zones and seasons) and can protect the DP primary and secondary containers against physical damage during simulated and/or real time shipping studies. Provide data to qualify your commercial shipping containers in your BLA submission.

3. We also remind you that while simulated shipping studies may be used in part to support your shipping validation, simulated studies alone are not sufficient to support shipping qualification. We recommend you perform real-time shipping studies under worst-case condition using DP representative of your commercial DP to confirm the results obtained from your simulated shipping studies.

4. The plunger movement study design appears adequate. Stopper movement should be measured during depressurization.

Discussion: The adequacy of the overall microbial control strategy, (b) (4) will be assessed during the BLA review and during the pre-license inspection. (b) (4)

Post-Meeting Comment: During the meeting, Fresenius proposed to provide real-time shipping protocol in the BLA and the Agency provided a tentative

agreement. We would like to clarify that the advice provided during the meeting was based on a misunderstanding regarding the shipping validation strategy proposal submitted by the sponsor in the presentation slides that were received by FDA shortly before the meeting. Therefore, we are clarifying that we do not agree to including the real-time shipping study results as a post-marketing commitment because shipping may impact container closure integrity of the prefilled syringes and may impact sterility of the final product. As indicated in the preliminary meeting comments, simulated studies alone are not sufficient to support shipping validation. Per the comments provided for the April 10, 2019 BPD Type 2 meeting, shipping validation study results should be provided as part of the complete application package at the time of BLA submission.

Question 2: (b) (4)

FDA Response to Question 2: (b) (4)

Refer to the draft guidance for industry entitled, "Development of Therapeutic Protein Biosimilars: Comparative Analytical Assessment and Other Quality-Related Considerations," (May 2019) available at https://www.fda.gov/media/125484/download for further information.

(b) (4)

Discussion: Fresenius proposed a strategy [redacted] (b) (4) **The Agency also referred to the comments provided in response to Question 2 above.**

Question 3:

a. *Comprehensive stability data to justify the shelf-life for the G-CSF intermediate, MSB11455 drug substance and MSB11455 drug product will be provided in the initial BLA submission. Does the Agency have any comments on the overall stability strategy?*

b. *Does the Agency agree that the stability studies comparing the stability profile of MSB11455-DP with US-Neulasta, together with comparative forced degradation study data are sufficient to support analytical similarity?*

FDA Response to Question 3:

a. According to ICHQ5C, expiration dating for the commercial DS and DP should be based on real time/real condition stability data of product for which its manufacture and storage are representative of the proposed commercial manufacturing scale of production. Your proposed shelf life of your G-CSF intermediate, DS and DP does not appear to be based on stability study results of material manufactured using the proposed commercial process, and you have not provided data and information to support that the lots used in the stability program were manufactured with a process representative of the commercial manufacturing process and are comparable to lots manufactured with the commercial scale process. In the BLA, provide data and information supporting that the lots used in the stability program were manufactured with a process representative of the commercial manufacturing process and are comparable to lots manufactured with the commercial scale process.

   In addition, it appears you did not conduct stress study at 40°C ± 2°C for your PPQ batches of G-CSF intermediate, MSB11455 DS and DP. Stress studies are important for establishing product comparability following changes to manufacturing processes or scale up. If changes are detected in the PPQ lots that raise uncertainty about the comparability of the PPQ lots to MSB11455 manufactured with earlier processes, stressed stability studies may address some of the potential uncertainty. Include a stress stability study in your stability program for the PPQ lots.

Discussion: The Agency emphasized that to support the shelf-life, the lots used in the stability studies need to be manufactured with a process representative of the commercial process and need to be comparable with the proposed

commercial material. In regard to the Agency's request to provide stressed stability studies at +40°C for the PPQ lots, Fresenius indicated that it would not be possible, as the PPQ lots are now beyond the proposed testing schedule, e.g. time 0, under stress condition. Fresenius proposed to provide the stress stability study data at +40°C on three lots of G-CSF, DS and DP as a PMC. The Agency clarified that the need of stress stability data is dependent on whether the proposed accelerated stability data at +25°C are able to clearly capture trends of all stability indicating quality attributes. The agency further stated that the lack of stress study results on PPQ lots at the time of BLA submission will not constitute a refuse-to-file issue, and the requirement for additional stress stability study will be determined as part of BLA review.

b. No, we do not agree. We have the following comments:

1. We note that you only tested a subset of quality attributes under each of your stress condition (e.g. HMW/Aggregate impurities under mechanical stress condition). We recommend that you perform an assessment on whether these chosen quality attributes under each stress condition represent all relevant stability indicating quality attributes which may result in evaluation of additional quality attributes (e.g., potency and charge variants etc.).

2. We also note that you did not include accelerated condition (25 ± 2ºC / 60 ± 5% RH) and stress condition (40 ± 2°C / 75 ± 5% RH) as part of your comparative stability study. Instead, you proposed to include thermal stress conditions (50°C ± 0.5°C for up to 15 days) in the comparative force degradation studies comparing the stability profile of MSB11455-DP with U.S.-licensed Neulasta in your BLA submission. We recommend that you justify whether the proposed thermal stress conditions (50°C ± 0.5°C for up to 15 days) would capture the trending of all relevant stability indicating quality attributes.

3. Your forced degradation studies utilized MSB11455-DP lots (BA024451P, BA024557P, BA024456P, BA040577P, BA039674P, and BA040407P). It appears that these DP lots were not manufactured from the proposed commercial DS and DP processes. Provide information to support that the manufacturing process for these DP lots is representative of the commercial scale process, and that these lots are comparable to DP lots manufactured with the commercial scale process.

The adequacy of the stability studies comparing the stability profile of MSB11455-DP with U.S.-licensed Neulasta will be a BLA review issue. Also, see preamble.

Discussion: **No further discussion**

Question 4: *Does the Agency agree with the proposed clinical package to be included in the initial 351(k) BLA for MSB11455?*

FDA Response to Question 4: The clinical package in general appears to be acceptable. However, a comprehensive summary of clinical safety and the rationale for not including an Integrated Summary of Safety should be provided in Module 2.7.4. The Module 5 should contain reports of supportive clinical studies including tables and datasets.

Discussion: No discussion.

Question 5: *Does the Agency concur with the strategy for the Integrated Summary of Immunogenicity (ISI) proposed to be included in the initial 351(k) BLA for MSB11455?*

FDA Response to Question 5: We generally agree with your strategy for the Integrated Summary of Immunogenicity (ISI) proposed to be included in the initial 351(k) BLA for MSB11455. We have the following comments:

1. Ensure that the description of your tiered bioanalytical testing strategy and methods includes links to method development and validation reports.
2. Provide traceability of drug product lots used in all your clinical studies.

Discussion: No discussion.

Question 6: *Does the Agency concur with the proposed selection of subject narratives and case report forms to be provided in the initial 351(k) BLA for MSB11455?*

FDA Response to Question 6: Your proposal appears to be acceptable. Narratives for each subject who died, experienced a serious adverse event, adverse events of special interest as pre-defined in the study management plan, discontinued due to adverse event should be provided for each clinical study. Any CRFs needed will be requested during review.

Discussion: No discussion.

Question 7: *Does the Agency concur that inclusion of a Risk Evaluation and Mitigation Strategy (REMS) for MSB11455 in the BLA submission will not be required?*

FDA Response to Question 7: Yes. The Agency agrees that inclusion of a REMS is not required for filing of your 351(k) BLA submission.

Discussion: No discussion.

Question 8: *Does the Agency agree with the proposal to include the following information in the initial BLA filing to fulfill the Office of Scientific Investigations (OSI)/Bioresearch Monitoring (BIMO) requirements?*

FDA Response to Question 8: Yes. We agree with your proposal.

Currently, there are no specific OSIS BIMO requirements for dataset specifications. Please submit the EMR200621-001 PK/PD dataset according to the current CDISC technical standards and include the ANC and analyte concentration data for individual subjects in the data listings.

Discussion: **No discussion.**

Question 9: *Does the Agency concur that the inclusion of a 4-month safety update for MSB11455 in the BLA submission will not be required?*

FDA Response to Question 9: No. The 4-month safety update should be submitted as per 21 CFR 314.50(d)(5).

Discussion: The Agency clarified that the 4-month safety update should contain any available new safety information the sponsor received since submission of the BLA. The Agency understands that there may not be much new information and if this is the case, the 4-month safety update would reflect that.

Question 10: *Does the Agency have any feedback on the Sponsor's approach to show compliance to 21CFR 312.120(b) for the two pivotal clinical studies in healthy volunteers that will be provided in the BLA?*

FDA Response to Question 10: All clinical studies conducted to support an indication should be submitted in Module 5. Clinical sites inspection will probably be required. The proposed approach to show compliance to 21CFR 312.120(b) for the two clinical studies appears reasonable. Adequacy of the information to support applicability of the foreign studies for the application will be a review issue.

Discussion: **No discussion.**

Question 11:

a) Does the Agency have any feedback on the proposed Table of Contents for MSB11455, a proposed biosimilar to US-licensed Neulasta?

b) Does the Agency have any additional comments on the adequacy of the proposed structure of the BLA?

FDA Response to Question 11: The proposed table of contents appears reasonable. See additional comments below:

> We note that you have provided in Table 1 of your meeting package the list of your manufacturing and quality control testing sites for MSB11455. However, you did not provide information on the site(s) for the comparative analytical assessment testing. Include this information in your BLA submission as part of your analytical similarity data package.

Discussion: No discussion.

Question 12: *Does the Agency have any feedback on the labeling concept for MSB11455 (Stimufend) based on FDA Draft Guidance for Industry – labeling for Biosimilar Products (March 2016), to support 351(k) BLA submission?*

FDA Response to Question 12: At this time, your labeling concept appears reasonable. We refer you to the more recent Guidance for industry – *Labeling for Biosimilar Products* (July 2018) https://www.fda.gov/media/96894/download

Discussion: No discussion.

Additional Clinical Pharmacology Comments:

Since ANC is the primary PD endpoint comparing test and reference products, you will be required to provide an analytical report for the evaluation of the absolute neutrophil count in Study EMR200621-001 as well as the in-study assay performance of the ANC assay. Validate the stability of neutrophils under the anticipated sampling handling conditions. Also, please note that run acceptance criteria should be established a priori and adhered to during study sample analysis. The acceptability of the analytical method for PD will be determined during the review of the proposed BLA. You should submit a comprehensive bioanalytical report in the proposed BLA which contains sufficient information to reconstruct the bioanalyses of study samples for ANC, including but not limited to the following:

- A description of the methods, and listing of the standard operating procedures (SOP) followed during analyses.
- Dates of receipt and identity of study samples and conditions of sample storage.
- Information on periodic calibration of the autoanalyzers.
- Information of quality controls (QC) used in the study (e.g., lots, levels, expiry)
- Description of the analytical run acceptance criteria.
- Tabular listing of analytical runs, including dates of analysis, subjects analyzed, the run status (accepted or rejected), and reason(s) for unsuccessful runs.
- Tabular listing of the QC results in the individual analytical runs.

- Tabular listing of samples reanalyzed (if any), reason for reanalysis, and final values reported.
- Description of any deviations from established procedures or any unexpected findings.

Discussion: No discussion.

Post-Meeting Response/Comment: In a November 8, 2019 e-mail, the Sponsor stated the following:

"The Sponsor would like to acknowledge the additional clinical pharmacology comment provided in the preliminary meeting responses and provide the following explanations.

The absolute neutrophil counts (ANC) for study EMR200621-001(Comparative single-dose PK/PD study in healthy subjects) were determined by the local laboratories affiliated to the clinical sites. Being diagnostic laboratories, the information listed in the additional comment was not compiled into a formal bioanalytical report, yet comprehensive documentation and data is available at the laboratories. The sponsor will include the information necessary to reconstruct the analysis of the study samples for ANC in module 2.7.1. of the BLA and include the relevant SOPs / procedures as references. As requested, the following topics will be covered:

- ***Description of the method and the instrumentation, including the predefined acceptance criteria and calibration procedures***
- ***Description of the QCs and the corresponding procedure***
- ***Description of the sample handling and justification of the sample stability***
- ***Description of the repeat analysis procedure"***

The Agency acknowledges your comment and the proposal appears reasonable at this time, but the final decision about the adequacy of the bioanalytical methods will be determined at the time of BLA review.

3.0 OTHER IMPORTANT INFORMATION

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed and the Sponsor had no further comments and questions after reviewing the language from the preliminary comments.

  All applications are expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application.

- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. You stated you intend to submit a complete application and therefore, there are no agreements for late submission of application components.

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain a pediatric assessment to support dosing, safety, and effectiveness of the product for the claimed indication unless this requirement is waived, deferred, or inapplicable.

Section 505B(l) of the FD&C Act, added by section 7002(d)(2) of the Affordable Care Act, provides that a biosimilar product that has not been determined to be interchangeable with the reference product is considered to have a "new active ingredient" for purposes of PREA, and a pediatric assessment is required unless waived, deferred, or inapplicable.

FDA encourages prospective biosimilar applicants to submit an initial pediatric study plan (iPSP) as early as practicable during product development. FDA recommends that you allow adequate time to reach agreement with FDA on the proposed iPSP prior to initiating your comparative clinical study.

Sections 505B(e)(2)(C) and 505B(e)(3) of the FD&C Act set forth a process lasting up to 210 days for reaching agreement with FDA on an iPSP. FDA encourages the sponsor to meet with FDA to discuss the details of the planned development program before submission of the iPSP. You must address PREA for every indication for which you seek licensure, and we encourage you to submit a comprehensive iPSP that addresses each indication. For indications for which the labeling for the reference product contains adequate pediatric information, you may be able to fulfill PREA requirements by satisfying the statutory requirements for biosimilarity and providing an adequate scientific justification for extrapolating the pediatric information from the reference product to your proposed product (see question and answer I.16 in FDA's draft guidance for industry on New and Revised Draft Q&As on Biosimilar Development and the BPCI Act (Revision 2) (December 2018). For conditions of use for which the reference product does not have adequate pediatric information in its labeling, a waiver (full or partial), or a deferral, may be appropriate if certain criteria are met.

After the iPSP is submitted, a sponsor must work with FDA to reach timely agreement on the plan, as required by section 505B(e)(2)-(3) of the FD&C Act. For additional guidance on the timing content, and submission of the iPSP,

including an iPSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email Pedsdrugs@fda.hhs.gov It should be noted that requested deferrals or waivers in the initial PSP will not be formally granted or denied until the product is licensed.

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d)[2] and 201.57[3] including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information[4] and Pregnancy and Lactation Labeling Final Rule[5] websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.

- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.

- Regulations and related guidance documents.

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[2] http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=201.56&utm_campaign=Google2&utm_source=fdaSearch&utm_medium=website&utm_term=21%20CFR%20201.56&utm_content=1

[3] http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=201.56&utm_campaign=Google2&utm_source=fdaSearch&utm_medium=website&utm_term=21%20CFR%20201.56&utm_content=1

[4] http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm 084159.htm

[5] http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307.htm

- A sample tool illustrating the format for Highlights and Contents, and

- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.

- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review and summary of the available published literature regarding the drug's use in pregnant and lactating women and the effects of the drug on male and female fertility (include search parameters and a copy of each reference publication), a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present), a summary of drug utilization rates amongst females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval, and an interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry. If you believe the information is not applicable, provide justification. Otherwise, this information should be located in Module 1. Refer to the draft guidance for industry *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format*.[6]

In addition, you should review the FDA guidance for industry *Labeling for Biosimilar Products* (July 2018).

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

NONPROPRIETARY NAME

On January 13, 2017, FDA issued a final guidance for industry *Nonproprietary Naming of Biological Products*, stating that, for certain biological products, the Agency intends to designate a proper name that includes a four-letter distinguishing suffix that is devoid of meaning.

Please note that certain provisions of this guidance describe a collection of information and are under review by the Office of Management and Budget under the Paperwork Reduction Act of 1995 (PRA). These provisions of the guidance describe the submission of proposed suffixes to the FDA, and a sponsor's related analysis of proposed suffixes, which are considered a "collection of information" under the PRA.

[6] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

FDA is not currently implementing provisions of the guidance that describe this collection of information.

However, provisions of the final guidance that do not describe the collection of information should be considered final and represent FDA's current thinking on the nonproprietary naming of biological products. These include, generally, the description of the naming convention (including its format for originator, related, and biosimilar biological products) and the considerations that support the convention.

Your proposed 351(k) BLA would be within the scope of this guidance. As such, FDA intends to assign a four-letter suffix for inclusion in the proper name designated in the license at such time as FDA approves the BLA.

MANUFACTURING FACILITIES

All facilities should be registered with FDA at the time of the 351(k) BLA submission and ready for inspection in accordance with 21 CFR 600.21 and 601.20(b)(2). Manufacturing and testing facilities will be subject to the cGMP standards as described in 21 CFR 601.20, including but not limited to the good manufacturing practice requirements set forth in 21 CFR 210, 211, and 600 of this chapter.

Manufacturing facilities should be in operation and manufacturing the product under review during the inspection. A manufacturing schedule for the drug substance and the drug product should be provided in Module 1 of the BLA to facilitate planning of pre-license/pre-approval inspections during the review cycle.

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
(1)				
(2)				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
(1)				
(2)				

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the items described in the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA ORA investigators who conduct those inspections. This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

Please refer to the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications*.

RECOMMENDATIONS FOR FORMATTING OF CLINICAL PHARMACOLOGY SUBMISSIONS FOR APPLICATIONS

If you are planning to include a clinical pharmacology study as part of your 351(k) BLA marketing application, we have the following general best practice recommendations for you to keep in mind as you prepare your submission, including guides for formatting your submission.

1. As it relates to clinical pharmacology-related sections of the application, apply the following advice when preparing the 351(k) BLA:
    a. Include the rationale for the selected dose used in the PK (and PD similarity, when applicable) study(ies) in the BLA (e.g., eCTD Module 2.7.2 Summary of Clinical Pharmacology).
    b. Include a summary evaluation of the impact of immunogenicity on the activity (e.g., efficacy/PD), safety, and pharmacokinetics, as is applicable, for the studies included in the BLA (e.g., eCTD Module 2.7.2 Summary of Clinical Pharmacology).
    c. Present the PK (and PD, when applicable) parameter data as geometric mean with coefficient of variation, mean ± standard deviation, and median with range in the study reports and throughout the BLA.
    d. Provide analysis data sets for all concentration-time and derived PK (and PD, when applicable) parameter datasets as SAS transport files (*.xpt). A description of each data item should be provided in a define.pdf file. Any concentrations or subjects that have been excluded from the analysis should be flagged and maintained in the datasets.
2. Include the following information in a tabular format in the 351(k) BLA for each of the completed clinical studies:
    a. Site number
    b. Principal investigator
    c. Site Location: Address (e.g., Street, City, State, Country) and contact information (i.e., phone, fax, email)
    d. Location of Principal Investigator: Address (e.g., Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.
3. Submit all PK (and PD, when applicable) bioanalytical method validation reports and bioanalytical study reports. In addition, complete the summary tables using the templates available in the 'Bioanalytical Methods Templates' Technical Specifications Document (https://www.fda.gov/media/131425/download) to provide the information regarding the bioanalytical methods for pharmacokinetic and/or biomarker assessments used in clinical pharmacology studies and their life-cycle information pertaining to the studies. Submit the tables in the Appendix of the Summary of Biopharmaceutics located in eCTD 2.7.1.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

No further issues requiring discussion were identified.

5.0 ACTION ITEMS

No action items were identified.

6.0 ATTACHMENTS AND HANDOUTS

Slides that were provided by the Sponsor and displayed during the meeting are attached.

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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

KATHY M ROBIE SUH
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